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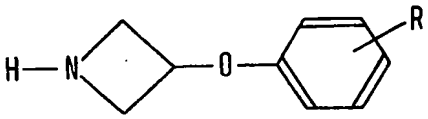
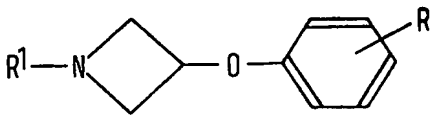
# (54) 3-Phenoxyazetidines

(57) 3-Phenoxyazetidines having the formula:



wherein R is hydrogen, aminocarbonyl or trifluoromethyl having central nervous system activity are disclosed.

Intermediates of the formula



wherein $R^1$ is α-methylbenzyl or diphenylmethyl are also claimed.

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The chemical formulæ appearing in the printed specification were submitted after the date of filing, the formulæ originally submitted being incapable of being satisfactorily reproduced.

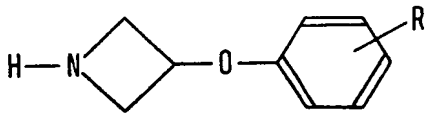
SPECIFICATION

**3-Phenoxyazetidines**

The present invention relates to certain novel heterocyclic compounds and more particularly to 3-phenoxyazetidines, compositions thereof, and methods of making and using same.

German Offenlengungsschrift 2.317.980 discloses N-oxides of N-substituted azetidine compounds and their use as intermediates for the preparation of 2-substituted isoxazolidines.

The invention is especially concerned with novel 3-phenoxyazetidine compounds having the formula:



wherein; R represents a hydrogen atom or an aminocarbinyl or trifluoromethyl group, and pharmaceutically acceptable acid addition salts thereof.

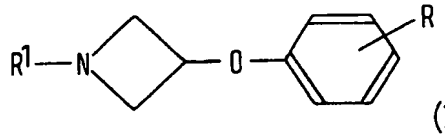
The compounds of Formula I are useful because of their pharmacological action on the central nervous system. In particular, the compounds have anorexigenic activity.

The anorexigenic property was determined according to the procedure of Roszkowski and Kelly, A Rapid Method for Assessing Drug Inhibition, J. Pharmacol. Exptl. Therap. *140*, 367–374 (1963) as modified by Alphin and Ward, Anorexigenic Effects of Fenfluramine Hydrochloride in Rats, Guinea Pigs and Dogs, Toxicology and Applied Pharmacology *14*, 182–191 (1969). Among the compounds of the present invention which have shown good activity in the aforementioned test is the representative compound 3-phenoxyazetidine.

It is, therefore, an object of the present invention to provide certain novel 3-phenoxyazetidines, compositions thereof, and methods of making and using the same. Another object is to provide novel 3-phenoxyazetidines having anorexigenic activity.

This invention also includes pharmaceutically acceptable acid addition salts of the compounds of Formula I. Such acid addition salts are easily prepared by methods known in the art and can be derived from various organic and inorganic acids such as citric, acetic, lactic, maleic, fumaric, benzoic, tartaric, ascorbic, pamoic, succinic, methanesulphonic, malic, citraconic, itaconic acid, hydrochloric, hydrobromic, sulphuric, phosphoric, nitric and related acids.

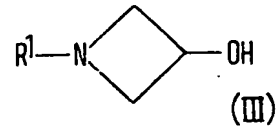
The compounds of the present invention may be conveniently prepared by contacting the appropriate 1-R¹-3-phenoxyazetidine of the formula:



(II)

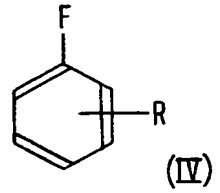
wherein R is defined as hereinbefore and R¹ represents an $\alpha$-methylbenzyl or diphenylmethyl group with hydrogen in the presence of a palladium on charcoal catalyst. The hydrogenolysis may be carried out in the presence of a lower alkanol solvent, ethanol being preferred. The rate of hydrogenolysis is dependent somewhat on time and temperature, a higher temperature generally decreasing the time required for complete hydrogenolysis. Typical times vary from about 3 hours to about 24 hours with typical temperature varying from about 70°C to about 90°C.

The starting material of Formula II may conveniently be prepared by contacting a 1-R¹-3-azetidinol of the formula:



(III)

wherein R ¹ is defined as hereinbefore with the appropriate fluorobenzene of the formula:



(IV)

wherein R represents a hydrogen or chloro atom or a trifluoromethyl group. The reaction is run at a temperature of from about 80°C to about 100°C and for a period of from about two hours to about five hours. The preferred solvent is dimethylformamide. The starting material of Formula II wherein R represents an aminocarbonyl group is preferably prepared by basic hydrolysis of a precursor cyano compound.

The compounds of Formula I and Formula II are basic compounds and are useful for neutralizing acidic solutions.

The following preparations and examples describe in detail compounds illustrative of the present invention and methods which have been devised for their preparation.

*Preparation 1*

*3-(3-Chlorophenoxy)-1-(α-methylbenzyl)azetidine Oxalate.*

1-(α-Methylbenzyl)-3-hydroxyazetidine maleate (393 g, 1.3 moles) was partitioned in dilute potassium hydroxide-benzene. The separated dried benzene solution was concentrated, the residual oil dissolved in 250 ml of dimethylformamide and added dropwise to a stirred suspension of 53 g (1.1 moles) of 50% sodium hydride in 750 ml of dimethylformamide at 90°C. The mixture was heated at 90°C for 1 hour and 130.5 g (1 mole) of 3-chlorofluorobenzene added dropwise at 90°C. The mixture was refluxed for 3 hours, cooled and partitioned between isopropyl ether and dilute sodium hydroxide. The isopropyl ether solution was dried, concentrated, and the residue added to 1200 ml of isopropyl alcohol containing 90 g (1 mole) of oxalic acid. The oxalate salt was recrystallized from ethanol. Yield 263 g (69%); m.p. 141–144°C.

| | | | | | |
|---|---|---|---|---|---|
| Analysis: | Calculated for $C_{19}H_{20}ClNO_5$: | C, 60.40; | H, 5.34; | N, 3.71 |
| | Found: | C, 60.19; | H, 5.55; | N, 3.60 |

*Preparation 2*

*1-(α-Methylbenzyl)-3-(4-trifluoromethylphenoxy)azetidine.*

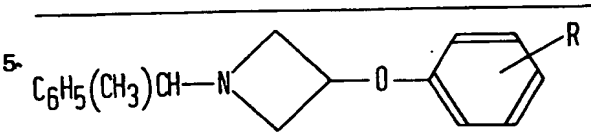
The maleate salt of 1-(α-methylbenzyl)-3-hydroxyazetidine (78.6 g, 0.20 mole) was partitioned between benzene and dilute sodium hydroxide, the benzene layer dried, filtered, and concentrated at reduced pressure. The residue was dissolved in 100 ml of dry dimethylformamide and added at a rapid dropwise rate, to a stirred suspension of 10.1 g (0.22 mole) of sodium hydride (50% in mineral oil) in 150 ml of dry dimethylformamide at 90°C. The solution was heated at 90°C for one hour and then treated dropwise with 32.0 g (0.20 mole) of 4-trifluoromethylfluorobenzene. The solution was refluxed for three hours. The cooled solution was partitioned between water and isopropyl ether, and the ether layer extracted with dilute hydrochloric acid. The aqueous acid layer was made basic with concentrated sodium hydroxide and ice, and extracted with isopropyl ether. The ether layer was concentrated and the residue distilled at 150–160°C/0.2 mm to give 25.6 g of product.

| | | | | | |
|---|---|---|---|---|---|
| Analysis: | Calculated for $C_{18}H_{18}F_3NO$: | C, 67.28; | H, 5.65; | N, 4.36 |
| | Found: | C, 67.27; | H, 5.84; | N, 4.34 |

*Preparations 3 to 7*

These were carried out according to the procedures set forth in detail in Preparations 1 and 2 by reacting 1-(α-methylbenzyl)-3-azetidinol with the appropriately substituted fluorobenzene. The physical constants and the R substituent are shown in Table I.

Table 1



| Preparation | R | M.P. (b.p.) °C | Salt |
|---|---|---|---|
| 3 | 2-$CONH_2$ | 148–52 | — |
| 4 | 4-CN | 65–8 | — |
| 5 | 3-$CF_3$ | 150–3 | $(COOH)_2$ |
| 6 | 2-$CF_3$ | 163–3 | $(COOH)_2$ |
| 7 | 3-CN | [1](185–90) | — |

[1]At 0.2 mm

The analytical data of Preparations 3 to 7 are shown in Table II.

Table II

Analytical Data on Preparations 3 to 7

| Preparation | Empirical Formula | Calculated C | Calculated H | Calculated N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|
| 3 | $C_{18}H_{20}N_2O_2$ | 72.95 | 6.80 | 9.45 | 72.56 | 6.78 | 9.32 |
| 4 | $C_{18}H_{18}N_2O$ | 77.67 | 6.52 | 10.06 | 77.61 | 6.53 | 10.01 |
| 5 | $C_{20}H_{20}F_3NO_5$ | 58.39 | 4.90 | 3.41 | 57.99 | 4.97 | 3.39 |
| 6 | $C_{20}H_{20}F_3NO_5$ | 58.39 | 4.90 | 3.41 | 58.15 | 4.89 | 3.37 |
| 7 | $C_{18}H_{18}N_2O$ | 77.67 | 6.52 | 10.06 | 77.32 | 6.54 | 9.87 |

*Preparation 8*

*3-[1-(α-Methylbenzyl)-3-azetidinyloxy]benzamide Oxalate.*

3-[1-(α-Methylbenzyl)-3-azetidinyloxy]benzonitrile 50.0 g; 0.18 mole) in 500 ml of t-butyl alcohol was treated with 50.0 g of finely ground potassium hydroxide. The mixture was stirred at reflux for 30 minutes. Ice and water were added to the reaction mixture and the organic layer was separated and dried over sodium sulphate. The dried filtered solution was concentrated at reduced pressure. The residue was dissolved in methanol and treated with an equivalent of oxalic acid, and the oxalate salt was recrystallized from ethanol to give 11.4 g (16%) of product, (m.p. 145°C).

Analysis: Calculated for $C_{20}H_{20}N_2O_6$: C, 62.17; H, 5.74; N, 7.25
Found: C, 62.17; H, 5.80; N, 7.20

*Preparation 9*

*4-[1-(α-Methylbenzyl)-3-azetidinyloxy]benzamide.*

To 45.0 g (0.16 mole) of 3-[1-(α-methylbenzyl)-3-azetidinyloxy]benzonitrile in 500 ml of t-butyl alcohl was added 45.0 g of finely ground potassium hydroxide. The mixture was stirred and refluxed for 30 minutes. Ice and water were added and a thick white solid separated. The solid was recrystallized from toluene to give 30.0 g (63%) of product melting at 174–178°C.

Analysis: Calculated for $C_{18}H_{20}N_2O_2$: C, 72.05; H, 6.80; N, 9.45
Found: C, 73.06; H, 6.79; H, 9.44

*Preparation 10*

*1-Diphenylmethyl-3-phenoxyazetidine.*

To a stirred suspension of 8.6 g (0.22 mole) of sodium amide in 100 ml of dry toluene was added 18.2 g (0.2 mole) of phenol in 50 ml of dry toluene. After stirring to 2 hours at 60°C the pot temperature was raised to 80°C and a solution of 1-diphenylmethyl-3-methylsulphonyloxyazetidine (63.4 g; 0.2 mole) in 200 ml of dry toluene was added dropwise. After an additional 2 hours at 80°C the cooled mixture was treated with water, the toluene layer was extracted with dilute sodium hydroxide solution, dried and concentrated at reduced pressure. The residue was crystallized twice from a water-isopropanol mixture. The free base melted at 83–85°C.

Analysis: Calculated for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44
Found: C, 83.69; H, 6.81; N, 4.41

*Example 1*
*4-(Phenoxy)azetidine Methanesulphonate.*

A 200 ml solution of 7.8 g (0.025 mole) of 1-diphenylmethyl-3-phenoxyazetidine in ethanol was treated with 20% Pd $(OH)_2$ on carbon and hydrogenated for 23 hours at about 45 psi and 80°C. The mixture was filtered and the filtrate concentrated. The residue was diluted to 30 ml with ethanol and 2.5 g of methanesulphonic acid added. The isolated methanesulphonate salt was recrystallized from ethanol. The salt weighed 2.3 g (37.5%) and melted at 128–130°C.

Analysis: Calculated for $C_{10}H_{15}NO_4S$: C, 48.97; H, 6.16; N, 5.71
Found: C, 48.40; H, 6.19; N, 5.63

The compound was also prepared by hydrogenolysis of 1-(α-methylbenzyl)-3-(3-chlorophenoxy)azetidine in isopropyl alcohol using the same type catalyst and conditions.

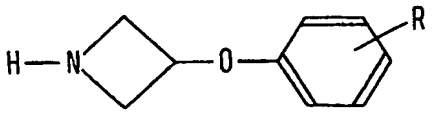
*Example 2*
*3-[4-(Trifluoromethyl)phenoxy]azetidine Oxalate.*

To 24.0 g (0.075 mole) of 3-[4-(trifluoromethyl)phenoxy]-1-(α-methylbenzyl)azetidine in 150 ml of ethanol was added 0.5 g of 20% Pd $(OH)_2$ on carbon, and the mixture was hydrogenated for five hours at 80°C and 45 psi. The mixture was cooled, filtered, and the filtrate concentrated at reduced pressure. The residue was dissolved in ethanol and treated with oxalic acid, and the oxalate salt was recrystallized three times in ethanol. The yield was 3.0 g (13%) and the salt melted at 176–178°C.

Analysis: Calculated for $C_{12}H_{12}F_3NO_3$: C, 46.91; H, 3.94; N, 4.56
Found: C, 47.07; H, 3.96; N, 4.59

Examples 3 to 7 were prepared according to the procedure set forth in detail in Examples 1 and 2 by hydrogenolysis of the α-methylbenzyl radical attached to the azetidine nitrogen. The physical constants and the R substituent are shown in Table 1.

Table 1




| Example | R | M.P. °C | Salt |
|---|---|---|---|
| 3 | 2-$CONH_2$ | 173–75 | $CH_3SO_3H$ |
| 4 | 3-$CF_3$ | 123–25 | [1]$C_6H_{11}NHSO_3H$ |
| 5 | 2-$CF_3$ | 154–56 | HCl |
| 6 | 3-$CONH_2$ | 160–63 | — |
| 7 | 4-$CONH_2$ | 187–88 | $(COOH)_2$ |

[1]N-cyclohexyl sulphamate

The analytical data of Examples 3 to 7 are shown in Table 2.

Table 2

Analytical Data on Examples 3 to 7

| Example | Empirical Formula | Calculated C | Calculated H | Calculated N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|
| 3 | $C_{11}H_{16}N_2O_5S$ | 45.82 | 5.59 | 9.72 | 45.48 | 5.65 | 9.45 |
| 4 | $C_{16}H_{23}F_3N_2O_4S$ | 48.48 | 5.85 | 7.07 | 48.08 | 5.94 | 6.97 |
| 5 | $C_{10}H_{11}ClF_3NO$ | 47.35 | 4.37 | 5.52 | 47.12 | 4.32 | 5.45 |
| 6 | $C_{10}H_{12}N_2O_2$ | 62.49 | 6.29 | 14.57 | 62.06 | 6.43 | 13.98 |
| 7 | $C_{12}H_{14}N_2O_6$ | 51.07 | 5.00 | 9.93 | 51.39 | 5.22 | 9.56 |

Effective quantities of any of the foregoing pharmacologically active 3-phenoxyazetidines may be administered to a living animal body orally as in capsules, tablets or elixirs. The free basic amino compounds, while effective, are preferably formulated and administered in the form of their pharmaceutically acceptable non-toxic acid addition salts.

Although very small quantities of the active materials of the present invention, even as low as one milligram, are effective when minor therapy is involved or in the cases of administration to subjects having a relatively low body weight, unit dosages are usually two milligrams or above and preferably five, ten, or twenty milligams. Five to ten milligrams appear optimum per unit dose, while usual broader ranges appear to be one to 20 milligrams per unit dose. The active agents of the invention may be combined with other pharmacologically active agents, or with buffers, antacids or the like, for administration and the proportion of the active agent in the composition may be varied widely. It is only necessary that the active ingredient constitute an effective amount; i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. Obviously, several unit dosage forms may be administered at about the same time.

Examples of compositions within the preferred ranges are given as follows:

Examples

*Examples 8A to 8C – Capsules*

Capsules of 5 mg (Example 8A), 10 mg (Example 8B), and 20 mg (Example 8C) of active ingredient per capsule were prepared; with the higher amounts of ingredient, reduction may be made in the amount of lactose.

| Typical blend for encapsulation | Per Capsule, mg |
|---|---|
| Active ingredient | 5.0 |
| Lactose | 296.7 |
| Starch | 129.0 |
| Magnesium stearate | 4.3 |
| Total | 435.0 mg |

The selected active ingredient is uniformly blended with the lactose, starch and magnesium stearate and the blend encapsulated.

*Example 9 – Tablets*

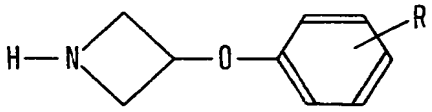
A typical formulation for a tablet containing 5.0 mg of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

| Ingredients | | Per Tablet, mg. |
|---|---|---|
| (1) | Active ingredient | 5.0 |
| (2) | Corn Starch | 13.6 |
| (3) | Corn starch (paste) | 3.4 |
| (4) | Lactose | 79.2 |
| (5) | Dicalcium phosphate | 68.0 |
| (6) | Calcium stearate | 0.9 |
| | Total | 170.1 mg. |

Ingredients 1, 2, 4 and 5 were uniformly blended. Ingredient 3 was prepared as a 10 percent paste in water. The blend was granulated with the starch paste and the wet mass was passed through a number eight mesh screen. The wet granulation was dried and passed through a number twelve mesh screen. The dried granules were blended with calcium stearate and compressed.

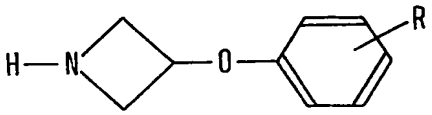
CLAIMS

1. 3-Phenoxyazetidines having the formula:



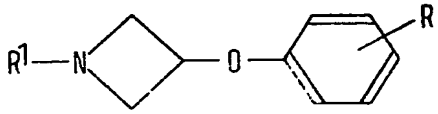
wherein: R represents a hydrogen or an aminocarbonyl or trifluoromethyl group, and pharmaceutically acceptable acid addition salts thereof.

2. 3-Phenoxyazetidine.
3. 3-(3-Trifluoromethyl)phenoxyazetidine.
4. 3-(4-Trifluoromethyl)phenoxyazetidine.
5. 3-(Phenoxy)azetidine methanesulphonate.
6. 3-[4-(Trifluoromethyl)phenoxy]azetidine oxalate.
7. 3-[2-(Aminocarbonyl)phenoxy]azetidine methanesulphonate.
8. 3-[3-(Trifluoromethyl)phenoxy]azetidine N-cyclohexylsulphamate.
9. 3-[2-(Trifluoromethyl)phenoxy]azetidine hydrochloride.
10. 3-[3-(Aminocarbonyl)phenoxy]azetidine.
11. 3-[4-(Aminocarbonyl)phenoxy]azetidine oxalate.
12. A process for the preparation of 3-phenoxyazetidines having the formula:



wherein:

R represents a hydrogen atom or an aminocarbonyl or trifluoromethyl group which comprises hydrogenolysis of a 1-$R^1$-3-phenoxyazetidine of the formula:



wherein:

$R^1$ represents an $\alpha$-methylbenzyl or diphenylmethyl group; and

R represents a hydrogen atom or an aminocarbonyl or trifluoromethyl group, using a palladium on carbon catalyst.

13. A process as claimed in Claim 12 substantially as specifically described herein with

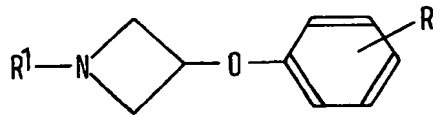
reference to any one of Examples 1 to 7.

14. A compound as claimed in Claim 1 whenever made by a process as claimed in Claim 12 or Claim 13.

15. A pharmaceutical composition comprising (a) two to twenty milligrams of a compound as claimed in any one of Claims 1 to 11 or 14, and (b) a pharmaceutically acceptable carrier or diluent therefor.

16. A compound as claimed in any one of Claims 1 to 11 or 14 for use in treating conditions where its anorexigenic effect is of benefit.

17. 1-$R^1$-3-phenoxyazetidines having the formula:



wherein:

$R^1$ represent an $\alpha$-methylbenzyl or diphenylmethyl group; and

R represents a hydrogen or a chloro atom or an aminocarbonyl, cyano or trifluoromethyl group.

18. A compound as claimed in Claim 17 and as specified in any one of Preparations 1 to 7.

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